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(54) **Process for the lactonization of mevinic acids and analogs thereof.**

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(56) References cited:
EP-A- 0 183 132
EP-A- 0 232 997

CHEMICAL ABSTRACTS, vol. 108, no. 5, February 1, 1988, Columbus, Ohio, USA LYNN, J.E. et al. "Synthesis of an HMG-CoA reductase inhibitor: a diastereoselective aldol approach" page 598, column 2, Abstract-no. 37 475h

(73) Proprietor: **MERCK & CO. INC.**
126, East Lincoln Avenue
P.O. Box 2000
Rahway New Jersey 07065-0900 (US)

(72) Inventor: **Treiber, Laszlo R.**
215 Morristown Road
Gillette New Jersey 07933 (US)

(74) Representative: **Cole, William Gwyn et al**
European Patent Department
Merck & Co., Inc.
Terlings Park
Eastwick Road
Harlow Essex CM20 2QR (GB)

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Description

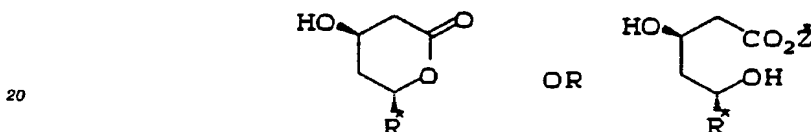
BACKGROUND OF THE INVENTION

5 Hypercholesterolemia is known to be one of the prime risk factors for ischemic cardiovascular disease, such as arteriosclerosis. Bile acid sequestrants have been used to treat this condition; they seem to be moderately effective but they must be consumed in large quantities, i.e. several grams at a time and they are not very palatable.

Mevacor® (lovastatin), now commercially available, is one of a group of very active antihypercholesterolemic agents that function by limiting cholesterol biosynthesis by inhibiting the enzyme, HMG-CoA reductase. In addition to the natural fermentation products, mevastatin and lovastatin, there are a variety of semi-synthetic and totally synthetic analogs thereof.

The naturally occurring compounds and their semi-synthetic analogs have the following general structural formulae:

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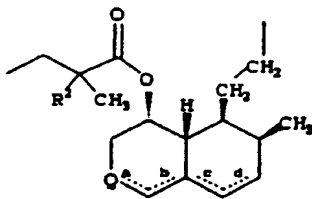


wherein:

25 Z* is hydrogen, C₁₋₅ alkyl or C₁₋₅ alkyl substituted with a member of the group consisting of phenyl, dimethylamino, or acetylamino; and R* is:

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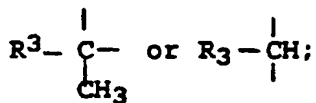
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wherein

40 Q is

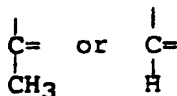
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R³ is H or OH; and

R² is hydrogen or methyl; and a, b, c, and d represent optional double bonds, especially where b and d represent double bonds or a, b, c, and d are all single bonds, provided that when a is a double bond, Q is

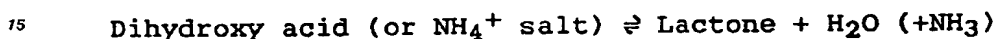
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The preparation of the naturally occurring compounds and their semi-synthetic analogs leads to a mixture of the lactone and dihydroxy acid forms. Mevacor® is marketed in the lactone form and thus it is of considerable importance to employ a high yield efficient method for the lactonization of the free acid or salt form. In the past, lactonization of the free acid or ammonium salt was effected by heating these substrates in a neutral organic solvent such as toluene, ethyl acetate, or isopropyl acetate at or near reflux. The lactonization is catalyzed by the presence of acid. The necessary acidity arises either through the ambient acidity of the substrate itself or by the addition of a stronger acid to effect lactonization at a lower temperature.

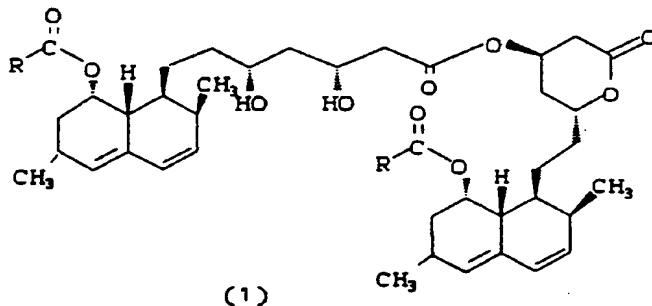
The use of conventional acid catalyzed lactonization in a neutral organic solvent to prepare HMG-CoA reductase inhibitors is described in published European patent application no. 0183132.

Lactonization is an equilibrium process, and in order to obtain a high yield of the lactone product, some means must be employed to shift the equilibrium to the lactone side of the equation:



In the prior procedures, lactonization is forced to near completion by removing the reaction by-products (water, ammonia) from the reaction mixture by means of azeotropic distillation and/or nitrogen sweep. The removal of water, and in the case of the ammonium salt ammonia, shifts the position of equilibrium to the lactone side.

Prior lactonization procedures exhibited several disadvantages. Typically the hydroxy acid substrate acted as the acid catalyst and thus as the substrate was consumed, the rate of reaction decreased requiring longer reaction times and allowing for increased by-product formation. Under the reaction conditions, the product 3-hydroxylactone is exposed for prolonged periods of time to the free acid which leads to increased amounts of a dimer (1) which results from an esterification reaction between the 3-hydroxyl group of the 3-hydroxylactone and the free acid.



The above dimer impurity has proved to be difficult to separate from the desired lactone product even with careful recrystallization techniques. The presence of the dimer, of course, lowers the overall yield and purity of the lactone product. Efforts to minimize the formation of the dimer have led to the use of high dilution in the lactonization reaction, however, this technique compromises the efficiency of the reaction.

A second impurity, resulting from dehydration of the 3-hydroxyl group on the lactone ring, was also observed using prior lactonization conditions. This impurity was likewise only inefficiently removed by recrystallization, resulting in diminished yields. The present invention alleviates this problem.

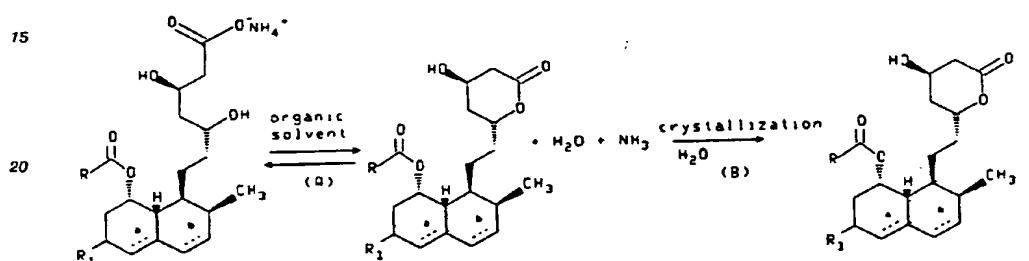
DETAILED DESCRIPTION OF THE INVENTION

The instant invention relates to a novel process for the conversion of mevinic acid HMG-CoA reductase inhibitors or analogs thereof into a lactone. The present process enables the shifting of the lactonization equilibrium by the continuous and selective removal of the lactone product from the reaction mixture. To employ this novel approach in the present lactonization equilibrium, it was necessary to identify a reaction medium in which the lactone product would be less soluble than the unlactonized starting material; and find a selective crystallization method for the removal of the lactone without entrainment of process impurities or

starting material.

Specifically the instant invention involves treating the free hydroxy acid or ammonium or metal salt derivative of a mevinic acid or analog thereof in an acetic acid medium, or other water miscible organic solvent which exhibits a sufficient solubility difference between the hydroxy acid and lactone, and a strong acid catalyst. After the free hydroxy acid-lactone equilibrium is established, water is gradually added in an amount sufficient to effect complete crystallization of the lactone from the reaction medium. This removal of the lactone continuously shifts the equilibrium to the lactone side and thus drives the lactonization to completion. In the instant procedure, the lactone is continuously removed from the reaction medium as it is formed, minimizing the lactone's exposure to the reaction conditions and thus minimizing the potential for its further reaction to form dimers. Thus one obtains a lactone product free from the impurities complicating the prior art lactonization procedures.

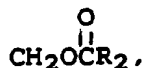
The instant invention can be depicted as:



wherein

R is C₁₋₁₀ alkyl;

R₁ is CH₃, CH₂OH,



CO₂R₃



OH, CH₂OR₂ or CH₂NR₄R₅;

R₂ is C₁₋₅ alkyl;

R₃ is H or C₁₋₅ alkyl;

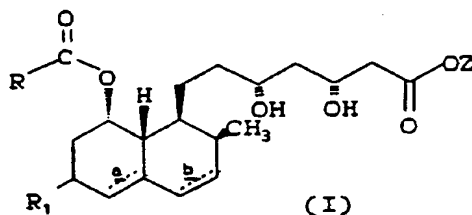
R₄ and R₅ are independently selected from H or C₁₋₁₀ alkyl;

a and b are both double bonds or one of a and b is a single bond or both a and b are single bonds.

Major advantages realized in the instant invention compared to the prior art are increased process productivity and product purity. The prior art procedures are conducted in a highly dilute medium (0.1M) in order to minimize dimer formation. The instant invention allows for lactonization at much higher concentrations (~24M) thus markedly improving productivity. Furthermore, the prior art procedure requires an additional step wherein the solvent is concentrated prior to isolation of the lactone; in the present procedure the lactone is isolated directly from the reaction mixture. Again the instant procedure demonstrates a greater efficiency than the prior art.

With respect to product purity, the prior art method yielded a semi-pure product which contained from 0.4 to 0.8% of a difficult-to-remove dimeric impurity, whereas the levels of this impurity under the present lactonization conditions is reduced to less than 0.2%.

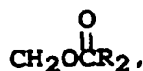
The specific hydroxy acids or salts derived therefrom, which are employed in the instant invention, are of structure (I):



wherein:

R is C₁₋₁₀ alkyl;

R₁ is CH₃, CH₂OH,



CO₂R₃,



OH, CH₂OR₂, or CH₂NR₄R₅;

Z is H or NH₄⁺ or a metal cation;

R₂ is C₁₋₅ alkyl;

R₃ is H or C₁₋₅ alkyl;

R₄ and R₅ are independently selected from H or C₁₋₅ alkyl;

a and b are both double bonds or one of a and b is a single bond or both a and b are single bonds.

The solvents employed are water miscible organic solvents. The particular solvent is determined by the characteristics of crystallization, i.e. the solubility difference between the hydroxy acid or salt and the lactone, the crystallization selectivity and the kinetics of crystallization, in the water-organic solvent mixture. Suitable solvents include acetic acid, acetonitrile, acetone and methanol preferably acetic acid, acetonitrile or acetone.

The rate of lactonization depends on the strength and concentration of the acid catalyst. Any inorganic or organic acid of acidity sufficient to catalyze the formation of a lactone may be employed. Illustrative of suitable acids which may be employed are formic, phosphoric, trifluoroacetic, sulfuric, hydrochloric, perchloric, p-toluenesulfonic and methanesulfonic acid.

The lactonization may be conducted over a temperature range of 20 °C to 30 °C, preferably 20-25 °C. It is critical that the temperature not be allowed to rise above 30 °C as this leads to increased by-product formation.

Preferred metal cations are cations of alkali metals, such as sodium or potassium, cations of alkaline earth metals, such as calcium or magnesium, or cations of other metals such as aluminum, iron, zinc, copper, nickel or cobalt. The alkali metal cations, alkaline earth metal cations, and aluminum cations are preferred; the sodium, calcium and aluminum cations being most preferred.

In one embodiment of the instant process is the compounds of formula (I) wherein:

R is C₁₋₁₀ alkyl,

R₁ is CH₃; and

Z is H or NH₄⁺.

In one class of this embodiment R is sec-butyl or 1,1-dimethylpropyl and R₁ is CH₃, Z is NH₄⁺, a and b are double bonds, the organic solvent is acetic acid, acetonitrile or acetone and the acid catalyst is trifluoroacetic acid or methanesulfonic acid. In one subclass R is 1,1-dimethylpropyl, the organic solvent is acetic acid and the acid catalyst is trifluoroacetic or methanesulfonic acid preferably methane sulfonic acid. In a second subclass, R is sec-butyl, the organic solvent is acetone, acetic acid or acetonitrile, and the acid catalyst is trifluoroacetic acid or methanesulfonic acid.

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The following examples illustrate the process of the instant invention and are not to be considered as limiting the invention set forth in the claims appended hereto.

EXAMPLE 1

Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1-(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one.

Ammonium 7-[1,2,6,7,8,8a(R)-hexahydro-2(S), 6(R)-dimethyl-8(S)-(2,2-dimethylbutyryloxy)-1(S)-naphthyl]-3(R),5(R)-dihydroxyheptanoate (12.5 grams, 97.9 wt. % purity by HPLC, 27.0 mmol) was stirred with a mixture of acetic acid (40 ml), water (20 ml) and trifluoroacetic acid (3.84 g, 33.7 mmol, 2.5 ml) under a nitrogen atmosphere for 3 hours at 23-26 °C.

After the 3 hour age period, the first portion of water (10 ml) was added at once. From that point on, the addition of the second portion of water (15 ml) was carried out uniformly over a period of 3 hours. The product lactone began crystallizing out during this time period.

The last portion of water (35 ml) was added over a period of 1 hour. The sample was then agitated for an additional 2 hours. The trifluoroacetic acid was neutralized with concentrated ammonium hydroxide (5.0 ml, 1.35 g NH₃, 79 mmol) which was added slowly with cooling of the batch mixture. The batch was then agitated for 1 hour and then the product filtered and washed with about 100 ml of an acetic acid-water mixture (1:2 v/v) followed by washing with 100 ml of water. The filter cake was dried to constant weight in vacuo at 35 °C under a slow nitrogen sweep to yield the titled compound in 98.0% purity (HPLC). The level of dimer was <0.2%.

EXAMPLE 2

Preparation of 6(R)-[2-[8(S)-(2,2-dimethylbutyryloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1-(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one.

Ammonium 7-1,2,6,7,8,8a(R)-hexahydro-(S),6(R)-dimethyl-8(S)-(2,2-dimethylbutyryloxy)-1(S)-naphthyl]-3(R),5(R)-dihydroxyheptanoate (12.5 g, 95.4 wt. % purity by HPLC, 27.6 mmol), and BHA (butylated hydroxy anisole) (0.075g) were suspended in a mixture of acetic acid (40 ml) and water (20 ml) at 22-25 °C under nitrogen. MSA (methanesulfonic acid) (2.94 g, 2.00 ml, 30.6 mmol) was added to the above suspension.

After 2 hours, water (10 ml) was added in one portion. From that point on, the addition of the second portion of water (15 ml) was carried out uniformly over a period of 3 hours. The last portion of water (35 ml) was added over a period of 1 hour, and the sample agitated for an additional hour. The methanesulfonic acid was neutralized with concentrated ammonium hydroxide (4.0 ml, 1.35 g NH₃, 63.2 mmol) which was added slowly with cooling of the batch mixture. The batch was then agitated for 1 hour, and then the product filtered and washed with about 100 ml of an acetic acid-water mixture (1:2 v/v) followed by washing with 100 ml of water. The filter cake was dried to constant weight in vacuo at 35 °C under a slow nitrogen sweep to yield the titled compound in 96.5% purity (HPLC). The level of dimer was <0.2%.

EXAMPLE 3

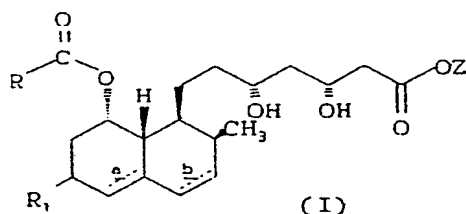
Preparation of 6(R)-[2-[8(S)-(2-methylbutyryloxy)-2 (S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1-(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one.

The titled compound is prepared following the procedure of Example 1 or Example 2 but substituting Ammonium 7-[1,2,6,7,8,8a(R)-hexahydro-(S),6(R)-dimethyl-8(S)-2-methylbutyryloxy)-1(S)-naphthyl]-3(R),5(R)-dihydroxyheptanoate as the substance to be lactonized. Alternatively acetone or acetonitrile may be substituted as the organic solvent, but with a neutral solvent, the acid is neutralized in the presence of a pH probe to pH 6.

Claims

Claims for the following Contracting States : DE, GB, FR, IT, NL, SE, CH, BE, AT, LU, LI

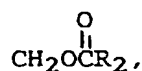
1. A process for the lactonization of a compound of structure (I):



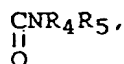
wherein:

R is C₁₋₁₀ alkyl;

R₁ is CH₃, CH₂OH,



CO₂R₃,



OH, CH₂OR₂, or CH₂NR₄R₅;

Z is H or NH₄⁺ or a metal cation;

R₂ is C₁₋₅ alkyl;

R₃ is H or C₁₋₅ alkyl;

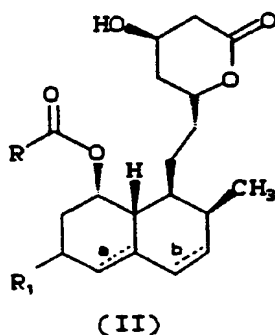
R₄ and R₅ are independently selected from H or C₁₋₅ alkyl;

a and b are both double bonds or one of a and b is a single bond or both a and b are single bonds;

which comprises:

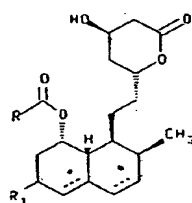
(A) treating (I) with a mixture of a water miscible organic solvent, water and an acid catalyst under an inert gas atmosphere for about 2-3 hours at 20-25 °C;

(B) treatment of the reaction mixture with additional water to precipitate the product lactone (II) as a crystalline mass.



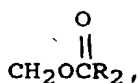
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2. A process according to Claim 1 wherein:
R is C₁₋₁₀ alkyl,
R₁ is CH₃; and
Z is H or NH₄ +.
3. A process according to Claim 2 wherein R is sec-butyl or 1,1-dimethylpropyl, and a and b are double bonds.
4. A process according to Claim 3 wherein the organic solvent is selected from acetic acid, acetonitrile or acetone.
5. A process according to Claim 4 wherein the acid catalyst is selected from: formic, phosphoric, trifluoroacetic, sulfuric, hydrochloric, perchloric, p-toluenesulfonic and methanesulfonic acid.
6. A process according to Claim 5 wherein R is 1,1-dimethylpropyl.
7. A process according to Claim 6 wherein the organic solvent is acetic acid and Z is NH₄ +.
8. A process according to Claim 7 wherein the acid catalyst is trifluoroacetic acid, or methanesulfonic acid.
9. A process according to Claim 8 wherein the acid catalyst is methanesulfonic acid.
10. A process according to Claim 5 wherein R is sec-butyl.
11. A process for the preparation of a compound of the structure (II):

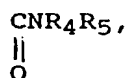


II

wherein:
R is C₁₋₁₀ alkyl;
R₁ is CH₃, CH₂OH,

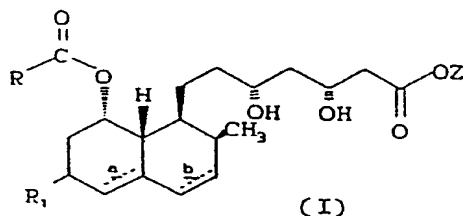


CO₂R₃,



OH, CH₂OR₂, or CH₂NR₄R₅;
Z is H or NH₄ + or a metal cation;
R₂ is C₁₋₅ alkyl;

R_3 is H or C_{1-5} alkyl;
 R_4 and R_5 are independently selected from H or C_{1-5} alkyl;
 \underline{a} and \underline{b} are both double bonds or one of \underline{a} and \underline{b} are single bonds;
 which comprises treating a compound of the structure (I)



wherein R , R_1 , \underline{a} and \underline{b} are defined in relation to structure (II) and wherein Z is H, NH_4^+ or a metal cation in a water miscible organic solvent with a strong acid catalyst and thereafter gradually adding water until crystallisation of the lactone from the reaction medium is effected, whereby the compound of structure (II) is produced containing less than 0.2% of dimeric impurity.

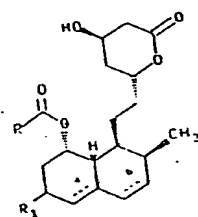
12. A process according to claim 11 wherein R is C_{1-10} alkyl, R_1 is CH_3 and Z is H^+ or NH_4^+ .

13. A process according to claim 11 wherein the solvent is acetic acid, acetonitrile or acetone.

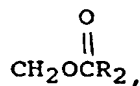
14. A process according to any of claims 11 to 13 wherein Z is NH_4^+ .

15. A process according to any of claims 11 to 14 wherein the strong acid catalyst is formic, phosphoric, trifluoroacetic, sulfuric, hydrochloric, perchloric p-toluenesulfonic or methanesulfonic.

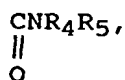
16. A compound of the structure (II)



wherein:
 R is C_{1-10} alkyl
 R_1 is CH_3 , CH_2OH ;



CO_2R_3



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OH, CH₂OR₂, or CH₂NR₄R₅;

Z is H or NH₄⁺ or a metal cation;

R₂ is C₁₋₅ alkyl;

R₃ is H or C₁₋₅ alkyl;

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R₄ and R₅ are independently selected from H or C₁₋₅ alkyl;

a and b are both double bonds or one of a and b is a single bond or both a and b are single bonds; containing less than 0.2% of dimeric impurity.

17. A compound according to claim 16 wherein R₁ is CH₃.

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18. A compound according to claim 16 wherein R₁ is OH.

19. A compound according to any of claim 16 to 18 wherein R is sec-butyl or 1,1-dimethylpropyl and a and b are double bonds.

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20. 6(R)-[2-[8(S)-(2,2-dimethylbutynyloxy)-2(S), 6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one containing less than 0.2% of dimeric impurity.

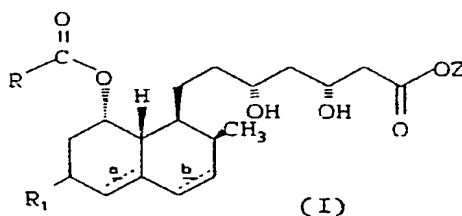
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21. 6(R)-[2-[8(S)-(S-methylbutyryloxy)-2(S), 6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one containing less than 0.2% of dimeric impurity.

Claims for the following Contracting States : ES, GR

1. A process for the lactonization of a compound of structure (I):

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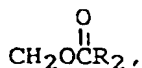
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wherein:

R is C₁₋₁₀ alkyl;

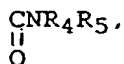
R₁ is CH₃, CH₂OH,

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CO₂R₃,



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OH, CH₂OR₂, or CH₂NR₄R₅;

Z is H or NH_4^+ or a metal cation;

R_2 is C_{1-5} alkyl;

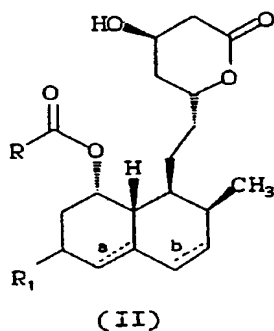
R_3 is H or C_{1-5} alkyl;

R_4 and R_5 are independently selected from H or C_{1-5} alkyl;

a and b are both double bonds or one of a and b is a single bond or both a and b are single bonds; which comprises:

(A) treating (I) with a mixture of a water miscible organic solvent, water and an acid catalyst under an inert gas atmosphere for about 2-3 hours at 20-25 °C;

(B) treatment of the reaction mixture with additional water to precipitate the product lactone (II) as a crystalline mass.



2. A process according to Claim 1 wherein:

R is C_{1-10} alkyl,

R_1 is CH_3 ; and

Z is H or NH_4^+ .

3. A process according to Claim 2 wherein R is sec-butyl or 1,1-dimethylpropyl, and a and b are double bonds.

4. A process according to Claim 3 wherein the organic solvent is selected from acetic acid, acetonitrile or acetone.

5. A process according to Claim 4 wherein the acid catalyst is selected from: formic, phosphoric, trifluoroacetic, sulfuric, hydrochloric, perchloric, p-toluenesulfonic and methanesulfonic acid.

6. A process according to Claim 5 wherein R is 1,1-dimethylpropyl.

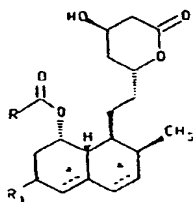
7. A process according to Claim 6 wherein the organic solvent is acetic acid and Z is NH_4^+ .

8. A process according to Claim 7 wherein the acid catalyst is trifluoroacetic acid, or methanesulfonic acid.

9. A process according to Claim 8 wherein the acid catalyst is methanesulfonic acid.

10. A process according to Claim 5 wherein R is sec-butyl.

11. A process for the preparation of a compound of the structure (II):

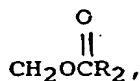


II

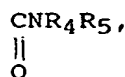
wherein:

R is C₁₋₁₀ alkyl;

R₁ is CH₃, CH₂OH,



CO₂R₃,



OH, CH₂OR₂, or CH₂NR₄R₅;

Z is H or NH₄⁺ or a metal cation;

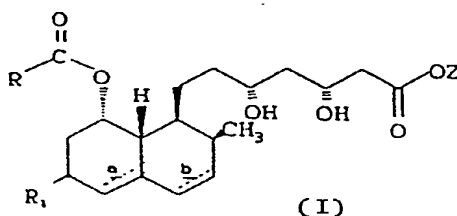
R₂ is C₁₋₅ alkyl;

R₃ is H or C₁₋₅ alkyl;

R₄ and R₅ are independently selected from H or C₁₋₅ alkyl;

a and b are both double bonds or one of a and b are single bonds;

which comprises treating a compound of the structure (I)



(I)

wherein R, R₁, a and b are defined in relation to structure (II) and wherein Z is H, NH₄⁺ or a metal cation in a water miscible organic solvent with a strong acid catalyst and thereafter gradually adding water until crystallisation of the lactone from the reaction medium is effected, whereby the compound of structure (II) is produced containing less than 0.2% of dimeric impurity.

12. A process according to claim 11 wherein R is C₁₋₁₀ alkyl, R₁ is CH₃ and Z is H⁺ or NH₄⁺.

13. A process according to claim 11 wherein the solvent is acetic acid, acetonitrile or acetone.

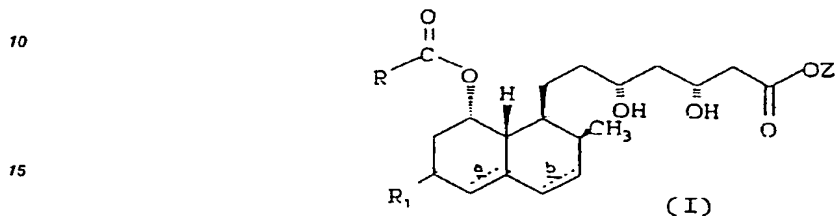
14. A process according to any of claims 11 to 13 wherein Z is NH₄⁺.

15. A process according to any of claims 11 to 14 wherein the strong acid catalyst is formic, phosphoric, trifluoroacetic, sulfuric, hydrochloric, perchloric p-toluenesulfonic or methanesulfonic.

Patentansprüche

5 Patentansprüche für folgende Vertragsstaaten : DE, GB, FR, IT, NL, SE, CH, BE, AT, LU, LI

1. Verfahren zur Lactonisierung einer Verbindung der Struktur (I):

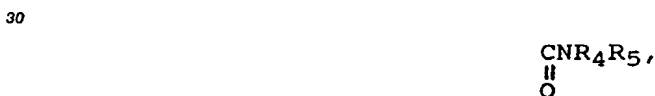


worin:

20 R für C₁-C₁₀-Alkyl steht;
R₁ für CH₃, CH₂OH,



CO₂R₃,



35 OH, CH₂OR₂ NR₄R₅ steht;

Z H, NH₄⁺ oder ein Metallkation bedeutet;

R₂ für C₁-5-Alkyl steht;

R₃ für H oder C₁-5-Alkyl steht;

R₄ und R₅ unabhängig ausgewählt werden aus H oder C₁-5-Alkyl;

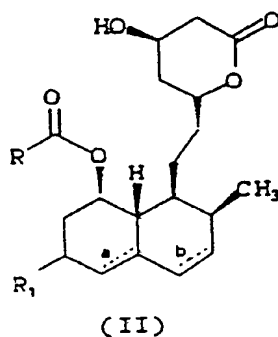
40 a und b beide Doppelbindungen darstellen oder eines von a und b eine Einfachbindung oder sowohl a als auch b Einfachbindungen darstellen, welches umfaßt:

(A) Behandeln von (I) mit einem Gemisch aus einem wassermischbaren organischen Lösungsmittel, Wasser und einem Säurekatalysator unter Inertgasatmosphäre etwa 2-3 Stunden lang bei 20-25 °C;

45 (B) Behandeln des Reaktionsgemisches mit zusätzlichem Wasser, um das Lactonprodukt (II) als kristalline Masse auszufällen.

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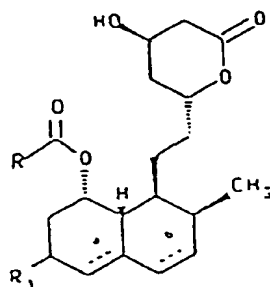
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2. Verfahren nach Anspruch 1, worin
R für C₁-₁₀-Alkyl steht,
R₁ für CH₃ steht und
Z für H oder NH₄⁺ steht.
3. Verfahren nach Anspruch 2, bei dem R für sec-Butyl oder 1,1-Dimethylpropyl steht und a und b Doppelbindungen darstellen.
4. Verfahren nach Anspruch 3, bei dem das organische Lösungsmittel ausgewählt wird aus Essigsäure, Acetonitril oder Aceton.
5. Verfahren nach Anspruch 4, bei dem der Säurekatalysator ausgewählt wird aus Ameisensäure, Phosphorsäure, Trifluoressigsäure, Schwefelsäure, Chlorwasserstoffsäure, Perchlorsäure, p-Toluolsulfonsäure und Methansulfonsäure.
6. Verfahren nach Anspruch 5, bei dem R 1,1-Dimethylpropyl bedeutet.
7. Verfahren nach Anspruch 6, bei dem das organische Lösungsmittel Essigsäure ist und Z für NH₄⁺ steht.
8. Verfahren nach Anspruch 7, bei dem der Säurekatalysator Trifluoressigsäure oder Methansulfonsäure ist.
9. Verfahren nach Anspruch 8, bei dem der Säurekatalysator Methansulfonsäure ist.
10. Verfahren nach Anspruch 5, bei dem R für sec-Butyl steht.
11. Verfahren zur Herstellung einer Verbindung der Struktur (II):

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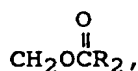


II

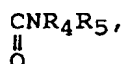
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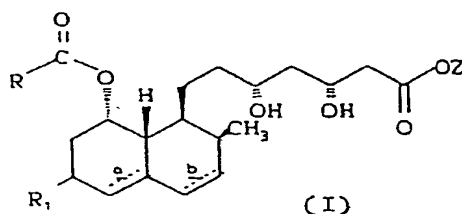
worin:
R für C₁-C₁₀-Alkyl steht;
R₁ für CH₃, CH₂OH,



CO₂R₃,



OH, CH₂OR₂ CH₂NR₄R₅ steht;
Z H, NH₄⁺ oder ein Metallkation bedeutet;
R₂ für C₁₋₅-Alkyl steht;
R₃ für H oder C₁₋₅-Alkyl steht;
R₄ und R₅ unabhängig ausgewählt werden aus H oder C₁₋₅-Alkyl;
a und b beide Doppelbindungen darstellen oder eines von a und b eine Einfachbindung darstellt;
welches umfaßt Behandeln einer Verbindung der Struktur (I),



worin R, R₁, a und b die bei Struktur (II) gegebenen Definitionen besitzen und worin Z für H, NH₄⁺ oder ein Metallkation steht, in einem wassermischbaren organischen Lösungsmittel mit einem stark sauren Katalysator und anschließend stufenweises Zugabe von Wasser, bis die Kristallisation des Lactons aus dem Reaktionsmedium erreicht worden ist, wobei die Verbindung der Struktur (II) so hergestellt wird, daß sie weniger als 0,2 % der dimeren Verunreinigung enthält.

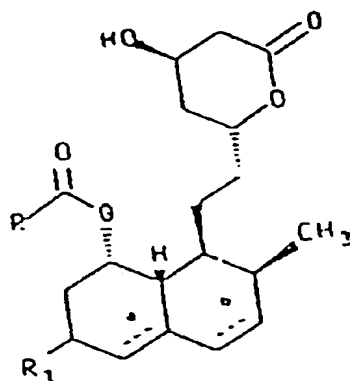
12. Verfahren nach Anspruch 11, bei dem R für C₁₋₁₀-Alkyl steht, R₁ CH₃ bedeutet und Z für H⁺ oder NH₄⁺ steht.

13. Verfahren nach Anspruch 11, bei dem das Lösungsmittel Essigsäure, Acetonitril oder Aceton ist.

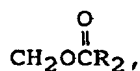
14. Verfahren nach einem der Ansprüche 11 bis 13, bei dem Z NH₄⁺ bedeutet.

15. Verfahren nach einem der Ansprüche 11 bis 14, bei dem der stark saure Katalysator Ameisensäure, Phosphorsäure, Trifluoressigsäure, Schwefelsäure, Chlorwasserstoffsäure, Perchlor-p-toluolsulfonsäure oder Methansulfonsäure ist.

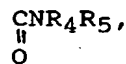
16. Verbindung der Struktur (II)



worin:
R für C₁-C₁₀-Alkyl steht;
R₁ für CH₃, CH₂OH,



CO₂R₃,



OH, CH₂OR₂, CH₂NR₄R₅ steht;
Z H, NH₄⁺ oder ein Metallkation bedeutet;
R₂ für C₁-C₅-Alkyl steht;
R₃ für H oder C₁-C₅-Alkyl steht;
R₄ und R₅ unabhängig ausgewählt werden aus H oder C₁-C₅-Alkyl;
a und b beide Doppelbindungen darstellen oder eines von a und b eine Einfachbindung oder sowohl a als auch b Einfachbindungen darstellen, die weniger als 0,2 % der dimeren Verunreinigung enthält.

17. Verbindung nach Anspruch 16, worin R₁ für CH₃ steht.

18. Verbindung nach Anspruch 16, worin R₁ für OH steht.

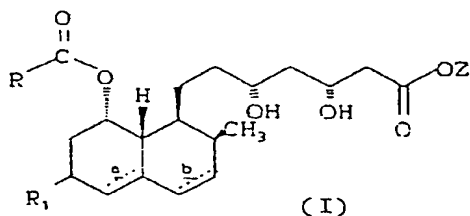
19. Verbindung nach einem der Ansprüche 16 bis 18, worin R für sec-Butyl oder 1,1-Dimethylpropyl steht und a und b Doppelbindungen darstellen.

20. 6(R)-[2-[8(S)-(2,2-Dimethylbutyloxy)-2(S), 6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]-ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-on, das weniger als 0,2 % der dimeren Verunreinigung enthält.

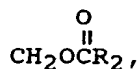
21. 6(R)-[2-[8(S)-(S-Methylbutyryloxy)-2(S), 6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S)]-ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-on, das weniger als 0,2 % der dimeren Verunreinigung enthält.

Patentansprüche für folgende Vertragsstaaten : ES, GR

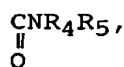
1. Verfahren zur Lactonisierung einer Verbindung der Struktur (I):



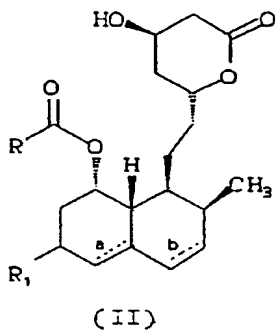
worin:
R für C₁-C₁₀-Alkyl steht;
R₁ für CH₃, CH₂OH,



CO₂R₃,



OH, CH₂OR₂ CH₂NR₄R₅ steht;
Z H, NH₄⁺ oder ein Metallkation bedeutet;
R₂ für C₁-₅-Alkyl steht;
R₃ für H oder C₁-₅-Alkyl steht;
R₄ und R₅ unabhängig ausgewählt werden aus H oder C₁-₅-Alkyl;
a und b beide Doppelbindungen darstellen oder eines von a und b eine Einfachbindung oder sowohl a als auch b Einfachbindungen darstellen, welches umfaßt:
(A) Behandeln von (I) mit einem Gemisch aus einem wassermischbaren organischen Lösungsmittel, Wasser und einem Säurekatalysator unter Inertgasatmosphäre etwa 2-3 Stunden lang bei 20-25 °C;
(B) Behandeln des Reaktionsgemisches mit zusätzlichem Wasser, um das Lactonprodukt (II) als kristalline Masse auszufällen.



2. Verfahren nach Anspruch 1, worin
R für C₁-C₁₀-Alkyl steht,
R₁ für CH₃ steht und
Z für H oder NH₄⁺ steht.

3. Verfahren nach Anspruch 2, bei dem R für sec-Butyl oder 1,1-Dimethylpropyl steht und a und b Doppelbindungen darstellen.

4. Verfahren nach Anspruch 3, bei dem das organische Lösungsmittel ausgewählt wird aus Essigsäure, Acetonitril oder Aceton.

5. Verfahren nach Anspruch 4, bei dem der Säurekatalysator ausgewählt wird aus Ameisensäure, Phosphorsäure, Trifluoressigsäure, Schwefelsäure, Chlorwasserstoffsäure, Perchlorsäure, p-Toluolsulfonsäure und Methansulfonsäure.

6. Verfahren nach Anspruch 5, bei dem R 1,1-Dimethylpropyl bedeutet.

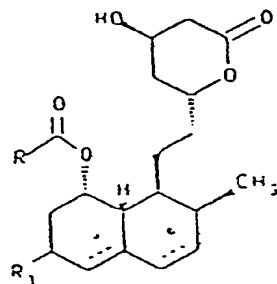
7. Verfahren nach Anspruch 6, bei dem das organische Lösungsmittel Essigsäure ist und Z für NH₄⁺ steht.

8. Verfahren nach Anspruch 7, bei dem der Säurekatalysator Trifluoressigsäure oder Methansulfonsäure ist.

9. Verfahren nach Anspruch 8, bei dem der Säurekatalysator Methansulfonsäure ist.

10. Verfahren nach Anspruch 5, bei dem R für sec-Butyl steht.

11. Verfahren zur Herstellung einer Verbindung der Struktur (II):

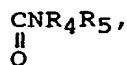
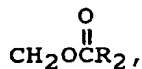


II

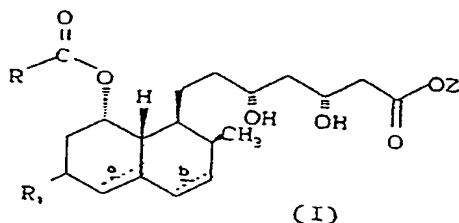
worin:

R für C₁-C₁₀-Alkyl steht;

R₁ für CH₃, CH₂OH,



OH, CH_2OR_2 , $\text{CH}_2\text{NR}_4\text{R}_5$ steht;
 Z H, NH_4^+ oder ein Metallkation bedeutet;
 R_2 für C_{1-5} -Alkyl steht;
 R_3 für H oder C_{1-5} -Alkyl steht;
 R_4 und R_5 unabhängig ausgewählt werden aus H oder C_{1-5} -Alkyl;
a und b beide Doppelbindungen darstellen oder eines von a und b eine Einfachbindung darstellt;
 welches umfaßt Behandeln einer Verbindung der Struktur (I),



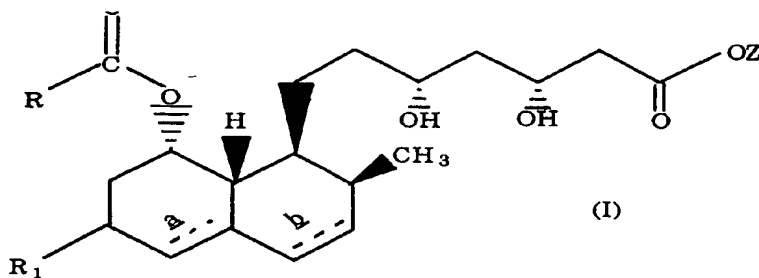
worin R, R_1 , a und b die bei Struktur (II) gegebenen Definitionen besitzen und worin Z für H, NH_4^+ oder ein Metallkation steht, in einem wassermischbaren organischen Lösungsmittel mit einem stark sauren Katalysator und anschließend stufenweises Zugabe von Wasser, bis die Kristallisation des Lactons aus dem Reaktionsmedium erreicht worden ist, wobei die Verbindung der Struktur (II) so hergestellt wird, daß sie weniger als 0,2 % der dimeren Verunreinigung enthält.

12. Verfahren nach Anspruch 11, bei dem R für C_{1-10} -Alkyl steht, R_1 CH_3 bedeutet und Z für H^+ oder NH_4^+ steht.
13. Verfahren nach Anspruch 11, bei dem das Lösungsmittel Essigsäure, Acetonitril oder Aceton ist.
14. Verfahren nach einem der Ansprüche 11 bis 13, bei dem Z NH_4^+ bedeutet.
15. Verfahren nach einem der Ansprüche 11 bis 14, bei dem der stark saure Katalysator Ameisensäure, Phosphorsäure, Trifluoressigsäure, Schwefelsäure, Chlorwasserstoffsäure, Perchlor-p-toluolsulfonsäure oder Methansulfonsäure ist.

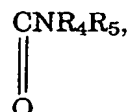
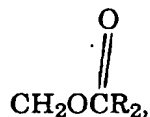
Revendications

Revendications pour les Etats contractants suivants : DE, GB, FR, IT, NL, SE, CH, BE, AT, LU, LI

1. Procédé de lactonisation d'un composé de structure (I) :



dans laquelle R est un alkyle en C_{1-10} ;
 R_1 est CH_3 , CH_2OH ,



OH, CH_2OR_2 ou $\text{CH}_2\text{NR}_4\text{R}_5$;

Z est H ou NH_4^+ ou un cation d'un métal ;

R_2 est un alkyle en $\text{C}_1\text{-C}_5$;

R_3 est H ou un alkyle en $\text{C}_1\text{-C}_5$;

R_4 et R_5 sont sélectionnés indépendamment parmi H ou un alkyle en $\text{C}_1\text{-C}_5$;

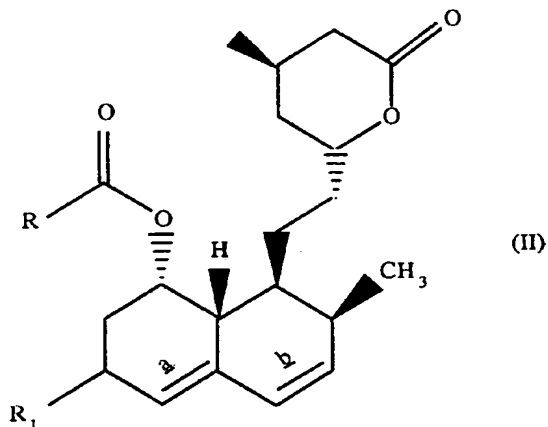
a et b sont tous les deux des doubles liaisons ou l'un de a et b est une liaison simple ou tous les deux

a et b sont des liaisons simples ;

qui comprend :

(A) le traitement (I) par un mélange d'un solvant organique miscible avec l'eau, d'eau et d'un catalyseur acide en atmosphère de gaz inerte pendant environ 2 à 3 heures à 20 à 25 °C.

(B) le traitement du mélange réactionnel avec de l'eau supplémentaire pour précipiter la lactone (II) du produit sous forme de masse cristalline



2. Procédé selon la revendication 1, dans lequel :

R est un alkyle en $\text{C}_1\text{-C}_{10}$;

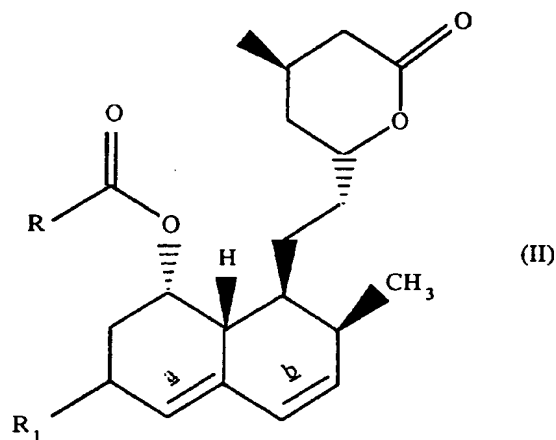
R_1 est CH_3 ; et

Z est H ou NH_4^+ .

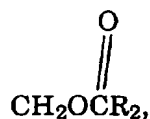
3. Procédé selon la revendication 2, dans lequel R est le sec-butyle ou le 1,1-diméthylpropyle, et a et b sont des doubles liaisons.

4. Procédé selon la revendication 3, dans lequel le solvant organique est sélectionné parmi l'acide acétique, l'acétonitrile ou l'acétone.

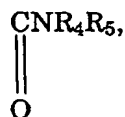
5. Procédé selon la revendication 4, dans lequel le catalyseur acide est sélectionné parmi : l'acide formique, phosphorique, trifluoroacétique, sulfurique, chlorhydrique, perchlorique, p-toluènesulfonique et méthanesulfonique.
6. Procédé selon la revendication 5, dans lequel R est le 1,1-diméthylpropyle.
7. Procédé selon la revendication 6, dans lequel le solvant organique est l'acide acétique et Z est NH_4^+ .
8. Procédé selon la revendication 7, dans lequel le catalyseur acide est l'acide trifluoroacétique ou l'acide méthanesulfonique.
9. Procédé selon la revendication 8, dans lequel le catalyseur acide est l'acide méthanesulfonique.
10. Procédé selon la revendication 5, dans lequel R est le sec-butyle.
11. Procédé pour la préparation d'un composé de la structure (II) :



dans laquelle R est un alkyle en $\text{C}_1\text{-C}_{10}$;
 R_1 est CH_3 , CH_2OH ,



CO_2R_3 ,



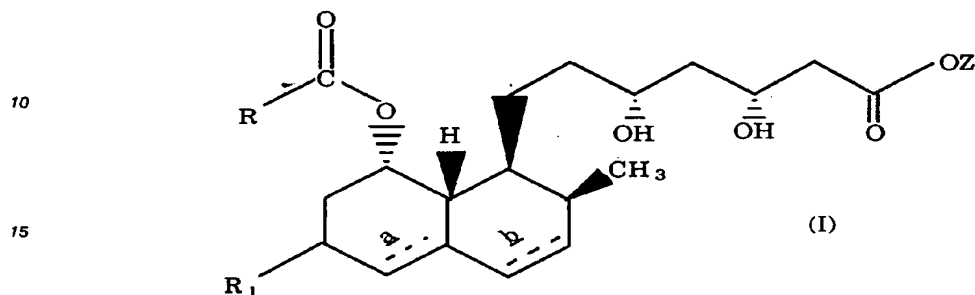
OH , CH_2OR_2 ou $\text{CH}_2\text{NR}_4\text{R}_5$;
 Z est H ou NH_4^+ ou un cation d'un métal ;
 R_2 est un alkyle en $\text{C}_1\text{-C}_5$;
 R_3 est H ou un alkyle en $\text{C}_1\text{-C}_5$;

R_4 et R_5 sont sélectionnés indépendamment parmi :

H ou un alkyle en C_1-C_5 ;

\underline{a} et \underline{b} sont tous les deux des doubles liaisons ou l'un de \underline{a} et \underline{b} est une liaison simple ;
qui comprend le traitement d'un composé de la structure (I)

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20 dans laquelle R , R_1 , \underline{a} et \underline{b} sont définis par rapport à la structure (II) et dans laquelle Z est H, NH_4^+ ou un cation d'un métal dans un solvant organique miscible avec l'eau avec un catalyseur d'acide fort, puis l'addition progressive d'eau jusqu'à ce que la cristallisation de la lactone du milieu réactionnel soit effectuée, ce qui permet la production du composé de la structure (II) contenant moins de 0,2 % d'impureté dimère.

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12. Procédé selon la revendication 11, dans lequel R est un alkyle en C_1-C_{10} , R_1 est CH_3 et Z est H^+ ou NH_4^+ .

13. Procédé selon la revendication 11, dans lequel le solvant est l'acide acétique, l'acétonitrile ou l'acétone.

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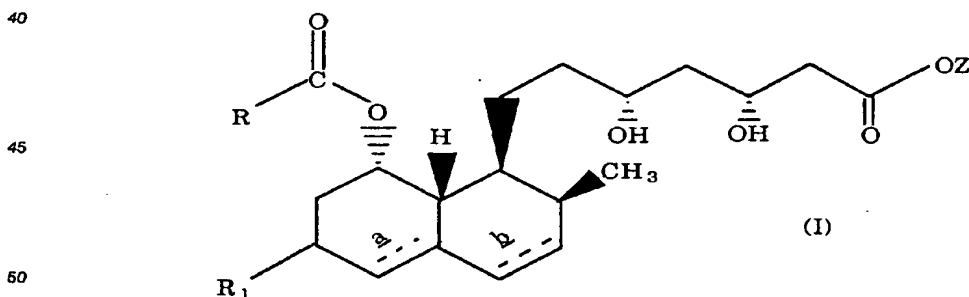
14. Procédé selon l'une quelconque des revendications 11 à 13, dans lequel Z est NH_4^+ .

15. Procédé selon l'une quelconque des revendications 11 à 14, dans lequel le catalyseur d'acide fort est formique, phosphorique, trifluoroacétique, sulfurique, chlorhydrique, perchlorique, p-toluènesulfonique ou méthanesulfonique.

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16. Composé de la structure (II) :

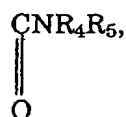
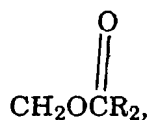
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dans laquelle R est un alkyle en C_1-C_{10} ;

R_1 est CH_3 , CH_2OH ,

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OH, CH_2OR_2 ou $\text{CH}_2\text{NR}_4\text{R}_5$;

Z est H ou NH_4^+ ou un cation d'un métal ;

R_2 est un alkyle en $\text{C}_1\text{-C}_5$;

R_3 est H ou un alkyle en $\text{C}_1\text{-C}_5$;

R_4 et R_5 sont sélectionnés indépendamment parmi :

H ou un alkyle en $\text{C}_1\text{-C}_5$;

a et b sont tous les deux des doubles liaisons ou l'un de a et b est une liaison simple ou tous les deux a et b sont des liaisons simples, contenant moins de 0,2 % d'impureté dimère.

17. Composé selon la revendication 16, dans lequel R_1 est CH_3 .

18. Composé selon la revendication 16, dans lequel R_1 est OH.

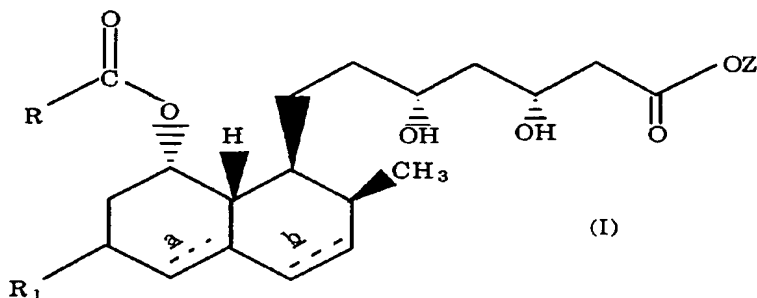
19. Composé selon l'une quelconque des revendications 16 à 18, dans lequel R est le sec-buitle ou le 1,1-diméthylpropyle et a et b sont des doubles liaisons.

20. Un 6(R)-[2-[8(S)-(2,2-diméthylbutynyloxy)-2(S),6(R)-diméthyl-1,2,6-7,8,8a(R)-hexahydronaphtyl-1(S)]-éthyl]-4(R)-hydroxy-3,4,5,6-tétrahydro-2H-pyranne-2, contenant moins de 0,2 % d'impureté dimère.

21. Un 6(R)-[2-[8(S)-(S-méthylbutyryloxy)-2(S),6(R)-diméthyl-1,2,6-7,8,8a(R)-hexahydronaphtyl-1(S)]-éthyl]-4(R)-hydroxy-3,4,5,6-tétrahydro-2H-pyranne-2, contenant moins de 0,2 % d'impureté dimère.

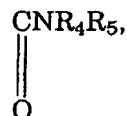
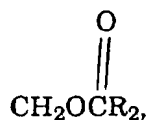
Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de lactonisation d'un composé de structure (I) :



dans laquelle R est un alkyle en $\text{C}_1\text{-C}_{10}$;

R_1 est CH_3 , CH_2OH ,



OH, CH_2OR_2 ou $\text{CH}_2\text{NR}_4\text{R}_5$;

Z est H ou NH_4^+ ou un cation d'un métal ;

R_2 est un alkyle en $\text{C}_1\text{-C}_5$;

R_3 est H ou un alkyle en $\text{C}_1\text{-C}_5$;

R_4 et R_5 sont sélectionnés indépendamment parmi H ou un alkyle en $\text{C}_1\text{-C}_5$;

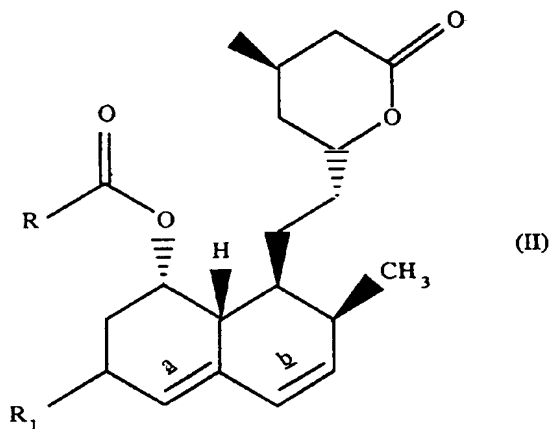
a et b sont tous les deux des doubles liaisons ou l'un de a et b est une liaison simple ou tous les deux

a et b sont des liaisons simples ;

qui comprend :

(A) le traitement (I) par un mélange d'un solvant organique miscible avec l'eau, d'eau et d'un catalyseur acide en atmosphère de gaz inerte pendant environ 2 à 3 heures à 20 à 25 °C.

(B) le traitement du mélange réactionnel avec de l'eau supplémentaire pour précipiter la lactone (II) du produit sous forme de masse cristalline



2. Procédé selon la revendication 1, dans lequel :

R est un alkyle en $\text{C}_1\text{-C}_{10}$;

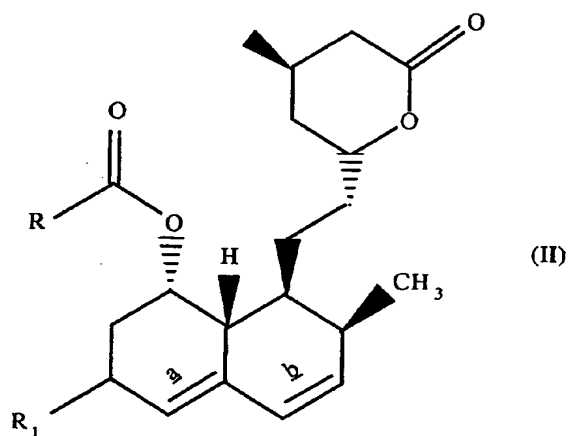
R_1 est CH_3 ; et

Z est H ou NH_4^+ .

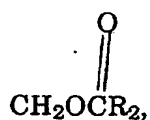
3. Procédé selon la revendication 2, dans lequel R est le sec-butyle ou le 1,1-diméthylpropyle, et a et b sont des doubles liaisons.

4. Procédé selon la revendication 3, dans lequel le solvant organique est sélectionné parmi l'acide acétique, l'acétonitrile ou l'acétone.

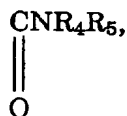
5. Procédé selon la revendication 4, dans lequel le catalyseur acide est sélectionné parmi : l'acide formique, phosphorique, trifluoroacétique, sulfurique, chlorhydrique, perchlorique, p-toluènesulfonique et méthanesulfonique.
6. Procédé selon la revendication 5, dans lequel R est le 1,1-diméthylpropyle.
7. Procédé selon la revendication 6, dans lequel le solvant organique est l'acide acétique et Z est NH_4^+ .
8. Procédé selon la revendication 7, dans lequel le catalyseur acide est l'acide trifluoroacétique ou l'acide méthanesulfonique.
9. Procédé selon la revendication 8, dans lequel le catalyseur acide est l'acide méthanesulfonique.
10. Procédé selon la revendication 5, dans lequel R est le sec-butyle.
11. Procédé pour la préparation d'un composé de la structure (II) :



dans laquelle R est un alkyle en $\text{C}_1\text{-C}_{10}$;
 R_1 est CH_3 , CH_2OH ,



CO_2R_3 ,



OH , CH_2OR_2 ou $\text{CH}_2\text{NR}_4\text{R}_5$;

Z est H ou NH_4^+ ou un cation d'un métal ;

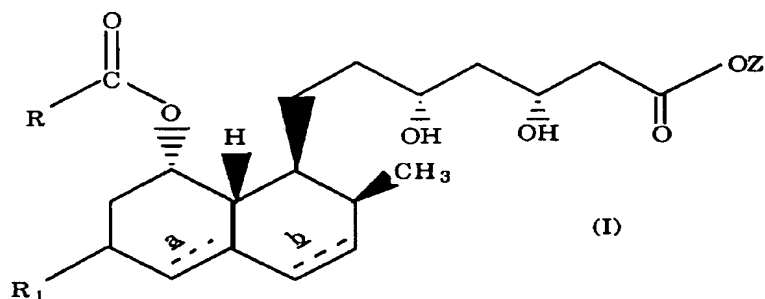
R_2 est un alkyle en $\text{C}_1\text{-C}_5$;

R_3 est H ou un alkyle en $\text{C}_1\text{-C}_5$;

R_4 et R_5 sont sélectionnés indépendamment parmi :

H ou un alkyle en C₁-C₅ ;

a et b sont tous les deux des doubles liaisons ou l'un de a et b est une liaison simple ;
qui comprend le traitement d'un composé de la structure (I)



dans laquelle R, R₁, a et b sont définis par rapport à la structure (II) et dans laquelle Z est H, NH₄⁺ ou un cation d'un métal dans un solvant organique miscible avec l'eau avec un catalyseur d'acide fort, puis l'addition progressive d'eau jusqu'à ce que la cristallisation de la lactone du milieu réactionnel soit effectuée, ce qui permet la production du composé de la structure (II) contenant moins de 0,2 % d'impureté dimère.

12. Procédé selon la revendication 11, dans lequel R est un alkyle en C₁-C₁₀, R₁ est CH₃ et Z est H⁺ ou NH₄⁺.

13. Procédé selon la revendication 11, dans lequel le solvant est l'acide acétique, l'acétonitrile ou l'acétone.

14. Procédé selon l'une quelconque des revendications 11 à 13, dans lequel Z est NH₄⁺.

15. Procédé selon l'une quelconque des revendications 11 à 14, dans lequel le catalyseur d'acide fort est formique, phosphorique, trifluoroacétique, sulfurique, chlorhydrique, perchlorique, p-toluènesulfonique ou méthanesulfonique.

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